

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **Stamm et al**

Application No.: **NOT YET ASSIGNED**

Filed: **July 6, 2001**

For: **FENOFIBRATE PHARMACEUTICAL COMPOSITION HAVING HIGH BIOAVAILABILITY AND METHOD FOR PREPARING IT**

Attorney Docket No: 107664.115US3

Assistant Commissioner of Patents  
Washington, DC 20231

**PRELIMINARY AMENDMENT**

Prior to consideration of the above application on the merits, please enter the following preliminary amendment, without prejudice.

**IN THE CLAIMS:**

Please cancel claims 1-34 without prejudice, and add new claims 35-56. A clean copy of the pending claims is set forth in Appendix 1. A marked-up copy of the claims showing the amendments is set forth in Appendix 2.

**IN THE SPECIFICATION:**

Please amend the specification at pages 1 and 23. A clean copy of the amended paragraphs at pages 1 and 23 is set forth in Appendix 3, and a marked-up copy showing the changes to the specification at pages 1 and 23 is set forth in Appendix 4.

**Remarks**

After entry of the amendment, claims 35-56 are pending in the application.

The specification has been amended to refer to the related applications and to amend the Abstract of the Disclosure. Added claims 35-56 are supported throughout

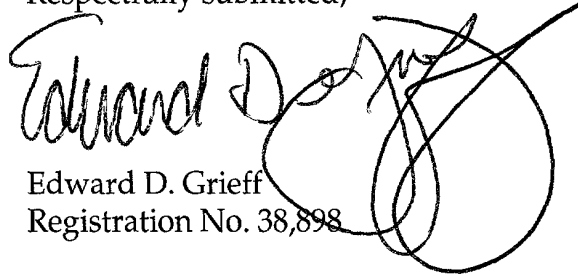
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Preliminary Amendment  
Continuation of U.S. Application No. 09/572,330

the specification. No issues of new matter should arise, and entry of the amendment is respectfully requested.

An early and favorable consideration and allowance of claims 35-56 is respectfully requested.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Edward D. Grieff", with a large circular flourish at the end.

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36. (New) The composition of claim 35, wherein the inert hydrosoluble carrier particles have a particle size between 50 and 500 microns.

38. (New) The composition of claim 37, wherein the inert hydrosoluble carrier particles are comprised of lactose.

40. (New) The composition of claim 39, wherein the granulates are produced by a fluidized-bed granulation technique.

42. (New) The composition of claim 35, wherein the immediate-release fenofibrate composition is in the form of a tablet.

43. (New) The composition of claim 35, further comprising a surfactant with the fenofibrate particles and the hydrophilic polymer.

## Appendix 1

44. (New) The composition of claim 35, wherein the hydrophilic polymer is polyvinylpyrrolidone.
45. (New) The composition according to claim 45, wherein the surfactant is sodium laurylsulfate.
46. (New) An immediate-release fenofibrate composition comprising granulates, said granulates comprising inert hydrosoluble carrier particles having a particle size between 100 and 400 microns, which are either isolated or agglomerated together, and fenofibrate particles with a particle size below 20 $\mu$ m in admixture with a hydrophilic polymer, adhering to the surface of the inert hydrosoluble carrier particles, wherein the granulates optionally comprise an outer coating or are optionally agglomerated, wherein the granulates are produced by fluidized-bed granulation which comprises spraying a suspension of fenofibrate particles with the hydrophilic polymer, and optionally a surfactant, onto the inert hydrosoluble carrier particles in a fluidized bed.
47. (New) The composition of claim 47, wherein the inert hydrosoluble carrier particles are comprised of lactose.
48. (New) The composition of claim 46, wherein the immediate-release fenofibrate composition is in the form of a tablet.
49. (New) The composition of claim 46, further comprising a surfactant with the fenofibrate particles and the hydrophilic polymer.
50. (New) The composition of claim 46, wherein the hydrophilic polymer is polyvinylpyrrolidone.
51. (New) The composition of claim 49, wherein the surfactant is sodium laurylsulfate.

## Appendix 1

52. (New) A method for preparing the composition of claim 1, comprising the steps of:

- (a) preparing a fenofibrate suspension in micronized form with a particle size below 20  $\mu\text{m}$  in a solution of a hydrophilic polymer, and optionally a surfactant;
- (b) spraying the fenofibrate suspension from step (a) to inert hydrosoluble carrier particles to form granules; and
- (c) optionally coating the granules from step (b) with one or several phase(s) or layer(s).

53. (New) The method of claim 52, wherein step (b) is carried out in a fluidized-bed granulator.

54. (New) The method of claim 52, further comprising compressing the product of step (b) or compressing the product of step (c).

55. (New) A method for preparing the composition of claim 46, comprising the steps of:

- (a) preparing a fenofibrate suspension in micronized form with a particle size below 20  $\mu\text{m}$  in a solution of a hydrophilic polymer, and optionally a surfactant;
- (b) spraying the fenofibrate suspension from step (a) to inert hydrosoluble carrier particles having a particle size between 100 and 400 microns to form granules in a fluidized-bed granulator; and
- (c) optionally coating the granules from step (b) with one or several phase(s) or layer(s).

56. (New) The method of claim 55, further comprising compressing the product of step (b) or compressing the product of step (c).

Figure 1. The effect of the concentration of the *Agaricus bisporus* spores on the growth of *Agaricus bisporus* and *Agaricus bisporus* spores. The concentration of the spores was 10<sup>6</sup> spores/ml (A), 10<sup>7</sup> spores/ml (B), 10<sup>8</sup> spores/ml (C), 10<sup>9</sup> spores/ml (D), 10<sup>10</sup> spores/ml (E), 10<sup>11</sup> spores/ml (F), 10<sup>12</sup> spores/ml (G), 10<sup>13</sup> spores/ml (H), 10<sup>14</sup> spores/ml (I), 10<sup>15</sup> spores/ml (J), 10<sup>16</sup> spores/ml (K), 10<sup>17</sup> spores/ml (L), 10<sup>18</sup> spores/ml (M), 10<sup>19</sup> spores/ml (N), 10<sup>20</sup> spores/ml (O), 10<sup>21</sup> spores/ml (P), 10<sup>22</sup> spores/ml (Q), 10<sup>23</sup> spores/ml (R), 10<sup>24</sup> spores/ml (S), 10<sup>25</sup> spores/ml (T), 10<sup>26</sup> spores/ml (U), 10<sup>27</sup> spores/ml (V), 10<sup>28</sup> spores/ml (W), 10<sup>29</sup> spores/ml (X), 10<sup>30</sup> spores/ml (Y), 10<sup>31</sup> spores/ml (Z), 10<sup>32</sup> spores/ml (AA), 10<sup>33</sup> spores/ml (AB), 10<sup>34</sup> spores/ml (AC), 10<sup>35</sup> spores/ml (AD), 10<sup>36</sup> spores/ml (AE), 10<sup>37</sup> spores/ml (AF), 10<sup>38</sup> spores/ml (AG), 10<sup>39</sup> spores/ml (AH), 10<sup>40</sup> spores/ml (AI), 10<sup>41</sup> spores/ml (AJ), 10<sup>42</sup> spores/ml (AK), 10<sup>43</sup> spores/ml (AL), 10<sup>44</sup> spores/ml (AM), 10<sup>45</sup> spores/ml (AN), 10<sup>46</sup> spores/ml (AO), 10<sup>47</sup> spores/ml (AP), 10<sup>48</sup> spores/ml (AQ), 10<sup>49</sup> spores/ml (AR), 10<sup>50</sup> spores/ml (AS), 10<sup>51</sup> spores/ml (AT), 10<sup>52</sup> spores/ml (AU), 10<sup>53</sup> spores/ml (AV), 10<sup>54</sup> spores/ml (AW), 10<sup>55</sup> spores/ml (AX), 10<sup>56</sup> spores/ml (AY), 10<sup>57</sup> spores/ml (AZ), 10<sup>58</sup> spores/ml (BA), 10<sup>59</sup> spores/ml (BB), 10<sup>60</sup> spores/ml (BC), 10<sup>61</sup> spores/ml (BD), 10<sup>62</sup> spores/ml (BE), 10<sup>63</sup> spores/ml (BF), 10<sup>64</sup> spores/ml (BG), 10<sup>65</sup> spores/ml (BH), 10<sup>66</sup> spores/ml (BI), 10<sup>67</sup> spores/ml (BJ), 10<sup>68</sup> spores/ml (BK), 10<sup>69</sup> spores/ml (BL), 10<sup>70</sup> spores/ml (BM), 10<sup>71</sup> spores/ml (BN), 10<sup>72</sup> spores/ml (BO), 10<sup>73</sup> spores/ml (BP), 10<sup>74</sup> spores/ml (BQ), 10<sup>75</sup> spores/ml (BR), 10<sup>76</sup> spores/ml (BS), 10<sup>77</sup> spores/ml (BT), 10<sup>78</sup> spores/ml (BU), 10<sup>79</sup> spores/ml (BV), 10<sup>80</sup> spores/ml (BW), 10<sup>81</sup> spores/ml (BX), 10<sup>82</sup> spores/ml (BY), 10<sup>83</sup> spores/ml (BZ), 10<sup>84</sup> spores/ml (CA), 10<sup>85</sup> spores/ml (CB), 10<sup>86</sup> spores/ml (CC), 10<sup>87</sup> spores/ml (CD), 10<sup>88</sup> spores/ml (CE), 10<sup>89</sup> spores/ml (CF), 10<sup>90</sup> spores/ml (CG), 10<sup>91</sup> spores/ml (CH), 10<sup>92</sup> spores/ml (CI), 10<sup>93</sup> spores/ml (CJ), 10<sup>94</sup> spores/ml (CK), 10<sup>95</sup> spores/ml (CL), 10<sup>96</sup> spores/ml (CM), 10<sup>97</sup> spores/ml (CN), 10<sup>98</sup> spores/ml (CO), 10<sup>99</sup> spores/ml (CP), 10<sup>100</sup> spores/ml (CQ), 10<sup>101</sup> spores/ml (CR), 10<sup>102</sup> spores/ml (CS), 10<sup>103</sup> spores/ml (CT), 10<sup>104</sup> spores/ml (CU), 10<sup>105</sup> spores/ml (CV), 10<sup>106</sup> spores/ml (CW), 10<sup>107</sup> spores/ml (CX), 10<sup>108</sup> spores/ml (CY), 10<sup>109</sup> spores/ml (CZ), 10<sup>110</sup> spores/ml (DA), 10<sup>111</sup> spores/ml (DB), 10<sup>112</sup> spores/ml (DC), 10<sup>113</sup> spores/ml (DD), 10<sup>114</sup> spores/ml (DE), 10<sup>115</sup> spores/ml (DF), 10<sup>116</sup> spores/ml (DG), 10<sup>117</sup> spores/ml (DH), 10<sup>118</sup> spores/ml (DI), 10<sup>119</sup> spores/ml (DJ), 10<sup>120</sup> spores/ml (DK), 10<sup>121</sup> spores/ml (DL), 10<sup>122</sup> spores/ml (DM), 10<sup>123</sup> spores/ml (DN), 10<sup>124</sup> spores/ml (DO), 10<sup>125</sup> spores/ml (DP), 10<sup>126</sup> spores/ml (DQ), 10<sup>127</sup> spores/ml (DR), 10<sup>128</sup> spores/ml (DS), 10<sup>129</sup> spores/ml (DT), 10<sup>130</sup> spores/ml (DU), 10<sup>131</sup> spores/ml (DV), 10<sup>132</sup> spores/ml (DW), 10<sup>133</sup> spores/ml (DX), 10<sup>134</sup> spores/ml (DY), 10<sup>135</sup> spores/ml (DZ), 10<sup>136</sup> spores/ml (EA), 10<sup>137</sup> spores/ml (EB), 10<sup>138</sup> spores/ml (EC), 10<sup>139</sup> spores/ml (ED), 10<sup>140</sup> spores/ml (EE), 10<sup>141</sup> spores/ml (EF), 10<sup>142</sup> spores/ml (EG), 10<sup>143</sup> spores/ml (EH), 10<sup>144</sup> spores/ml (EI), 10<sup>145</sup> spores/ml (EJ), 10<sup>146</sup> spores/ml (EK), 10<sup>147</sup> spores/ml (EL), 10<sup>148</sup> spores/ml (EM), 10<sup>149</sup> spores/ml (EN), 10<sup>150</sup> spores/ml (EO), 10<sup>151</sup> spores/ml (EP), 10<sup>152</sup> spores/ml (EQ), 10<sup>153</sup> spores/ml (ER), 10<sup>154</sup> spores/ml (ES), 10<sup>155</sup> spores/ml (ET), 10<sup>156</sup> spores/ml (EU), 10<sup>157</sup> spores/ml (EV), 10<sup>158</sup> spores/ml (EW), 10<sup>159</sup> spores/ml (EX), 10<sup>160</sup> spores/ml (EY), 10<sup>161</sup> spores/ml (EZ), 10<sup>162</sup> spores/ml (FA), 10<sup>163</sup> spores/ml (FB), 10<sup>164</sup> spores/ml (FC), 10<sup>165</sup> spores/ml (FD), 10<sup>166</sup> spores/ml (FE), 10<sup>167</sup> spores/ml (FF), 10<sup>168</sup> spores/ml (FG), 10<sup>169</sup> spores/ml (FH), 10<sup>170</sup> spores/ml (FI), 10<sup>171</sup> spores/ml (FJ), 10<sup>172</sup> spores/ml (FK), 10<sup>173</sup> spores/ml (FL), 10<sup>174</sup> spores/ml (FM), 10<sup>175</sup> spores/ml (FN), 10<sup>176</sup> spores/ml (FO), 10<sup>177</sup> spores/ml (FP), 10<sup>178</sup> spores/ml (FQ), 10<sup>179</sup> spores/ml (FR), 10<sup>180</sup> spores/ml (FS), 10<sup>181</sup> spores/ml (FT), 10<sup>182</sup> spores/ml (FU), 10<sup>183</sup> spores/ml (FV), 10<sup>184</sup> spores/ml (FW), 10<sup>185</sup> spores/ml (FX), 10<sup>186</sup> spores/ml (FY), 10<sup>187</sup> spores/ml (FZ), 10<sup>188</sup> spores/ml (GA), 10<sup>189</sup> spores/ml (GB), 10<sup>190</sup> spores/ml (GC), 10<sup>191</sup> spores/ml (GD), 10<sup>192</sup> spores/ml (GE), 10<sup>193</sup> spores/ml (GF), 10<sup>194</sup> spores/ml (GG), 10<sup>195</sup> spores/ml (GH), 10<sup>196</sup> spores/ml (GI), 10<sup>197</sup> spores/ml (GJ), 10<sup>198</sup> spores/ml (GK), 10<sup>199</sup> spores/ml (GL), 10<sup>200</sup> spores/ml (GM), 10<sup>201</sup> spores/ml (GN), 10<sup>202</sup> spores/ml (GO), 10<sup>203</sup> spores/ml (GP), 10<sup>204</sup> spores/ml (GQ), 10<sup>205</sup> spores/ml (GR), 10<sup>206</sup> spores/ml (GS), 10<sup>207</sup> spores/ml (GT), 10<sup>208</sup> spores/ml (GU), 10<sup>209</sup> spores/ml (GV), 10<sup>210</sup> spores/ml (GW), 10<sup>211</sup> spores/ml (GX), 10<sup>212</sup> spores/ml (GY), 10<sup>213</sup> spores/ml (GZ), 10<sup>214</sup> spores/ml (HA), 10<sup>215</sup> spores/ml (HB), 10<sup>216</sup> spores/ml (HC), 10<sup>217</sup> spores/ml (HD), 10<sup>218</sup> spores/ml (HE), 10<sup>219</sup> spores/ml (HF), 10<sup>220</sup> spores/ml (HG), 10<sup>221</sup> spores/ml (HH), 10<sup>222</sup> spores/ml (HI), 10<sup>223</sup> spores/ml (HJ), 10<sup>224</sup> spores/ml (HK), 10<sup>225</sup> spores/ml (HL), 10<sup>226</sup> spores/ml (HM), 10<sup>227</sup> spores/ml (HN), 10<sup>228</sup> spores/ml (HO), 10<sup>229</sup> spores/ml (HP), 10<sup>230</sup> spores/ml (HQ), 10<sup>231</sup> spores/ml (HR), 10<sup>232</sup> spores/ml (HS), 10<sup>233</sup> spores/ml (HT), 10

Cancel claims 1-34 without prejudice.

35. (New) An immediate-release fenofibrate composition comprising granulates, wherein said granulates comprise inert hydrosoluble carrier particles, which are either isolated or agglomerated together, and fenofibrate particles with a particle size below 20µm in admixture with a hydrophilic polymer adhering to the surface of the inert hydrosoluble carrier particles, wherein the granulates optionally comprise an outer coating or are optionally agglomerated.

36. (New) The composition of claim 35, wherein the inert hydrosoluble carrier particles have a particle size between 50 and 500 microns.

37. (New) The composition of claim 36, wherein the inert hydrosoluble carrier particles have a particle size between 100 and 400 microns.

38. (New) The composition of claim 37, wherein the inert hydrosoluble carrier particles are comprised of lactose.

39. (New) The composition of claim 35, wherein the granulates are produced by a process comprising spraying a suspension of the fenofibrate particles onto the inert hydrosoluble carrier particles.

40. (New) The composition of claim 39, wherein the granulates are produced by a fluidized-bed granulation technique.

41. (New) The composition of claim 40, wherein the fluidized-bed granulation technique comprises spraying a suspension of the fenofibrate particles with the hydrophilic polymer, and optionally a surfactant, onto the inert hydrosoluble carrier particles in a fluidized bed.

42. (New) The composition of claim 35, wherein the immediate-release fenofibrate composition is in the form of a tablet.

43. (New) The composition of claim 35, further comprising a surfactant with the fenofibrate particles and the hydrophilic polymer.

## Appendix 2

44. (New) The composition of claim 35, wherein the hydrophilic polymer is polyvinylpyrrolidone.
45. (New) The composition according to claim 45, wherein the surfactant is sodium laurylsulfate.
46. (New) An immediate-release fenofibrate composition comprising granulates, said granulates comprising inert hydrosoluble carrier particles having a particle size between 100 and 400 microns, which are either isolated or agglomerated together, and fenofibrate particles with a particle size below 20µm in admixture with a hydrophilic polymer, adhering to the surface of the inert hydrosoluble carrier particles, wherein the granulates optionally comprise an outer coating or are optionally agglomerated, wherein the granulates are produced by fluidized-bed granulation which comprises spraying a suspension of fenofibrate particles with the hydrophilic polymer, and optionally a surfactant, onto the inert hydrosoluble carrier particles in a fluidized bed.
47. (New) The composition of claim 47, wherein the inert hydrosoluble carrier particles are comprised of lactose.
48. (New) The composition of claim 46, wherein the immediate-release fenofibrate composition is in the form of a tablet.
49. (New) The composition of claim 46, further comprising a surfactant with the fenofibrate particles and the hydrophilic polymer.
50. (New) The composition of claim 46, wherein the hydrophilic polymer is polyvinylpyrrolidone.
51. (New) The composition of claim 49, wherein the surfactant is sodium laurylsulfate.

## Appendix 2

52. (New) A method for preparing the composition of claim 1, comprising the steps of:

(a) preparing a fenofibrate suspension in micronized form with a particle size below 20  $\mu\text{m}$  in a solution of a hydrophilic polymer, and optionally a surfactant;

(b) spraying the fenofibrate suspension from step (a) to inert hydrosoluble carrier particles to form granules; and

(c) optionally coating the granules from step (b) with one or several phase(s) or layer(s).

53. (New) The method of claim 52, wherein step (b) is carried out in a fluidized-bed granulator.

54. (New) The method of claim 52, further comprising compressing the product of step (b) or compressing the product of step (c).

55. (New) A method for preparing the composition of claim 46, comprising the steps of:

(a) preparing a fenofibrate suspension in micronized form with a particle size below 20  $\mu\text{m}$  in a solution of a hydrophilic polymer, and optionally a surfactant;

(b) spraying the fenofibrate suspension from step (a) to inert hydrosoluble carrier particles having a particle size between 100 and 400 microns to form granules in a fluidized-bed granulator; and

(c) optionally coating the granules from step (b) with one or several phase(s) or layer(s).

56. (New) The method of claim 55, further comprising compressing the product of step (b) or compressing the product of step (c).



### **Appendix 3 - Clean Copy of Specification**

The following paragraph has been inserted in the specification at page 1, line 2:

#### **Related Applications**

The present application is a continuation of Application No. 09/572,330 filed May 18, 2000, allowed, which is a continuation of Application No. 09/005,128 filed January 9, 1998, issued as U.S. Patent No. 6,074,670, which claims priority to French Application No. 97 00479 filed January 17, 1997.

The following paragraph has been inserted in the specification at page 23, lines 3-14:

The invention provides immediate-release fenofibrate compositions comprising granulates, where the granulates comprise inert hydrosoluble carrier particles, and particles of fenofibrate with a particle size below 20  $\mu\text{m}$  and hydrophilic polymer adhering to the carrier particles surface. The invention also provides methods for preparing the compositions.

#### Appendix 4 - Marked-Up Copy of Specification

Amend the specification at page 1 by inserting the following paragraph at line 2:

##### Related Applications

The present application is a continuation of Application No. 09/572,330 filed May 18, 2000, allowed, which is a continuation of Application No. 09/005,128 filed January 9, 1998, issued as U.S. Patent No. 6,074,670, which claims priority to French Application No. 97 00479 filed January 17, 1997.

Amend the specification at page 23, lines 3-14 as follows:

The invention provides immediate-release fenofibrate compositions comprising granulates, where the granulates comprise inert hydrosoluble carrier particles, and particles of fenofibrate with a particle size below 20  $\mu\text{m}$  and hydrophilic polymer adhering to the carrier particles surface. The invention also provides methods for preparing the compositions. The invention provides an immediate-release fenofibrate composition comprising (a) an inert hydrosoluble carrier covered with at least one layer containing fenofibrate in a micronized form havin a size less than 20  $\mu\text{m}$ , a hydrophilic polymer and, optionally, a surfactant, the polymer making up at least 20% by weight of (a); and (b) optionally one or several outer phase(s) or layer(s). The invention also provides a method for preparing said composition. Fig.1.